REMARKS

Claims 1 and 3-41 are pending in the application. Claims 17-37 are withdrawn as being drawn to non-elected inventions. Claims 1, 3-16, and 38-41 are under active consideration.

Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 103

Claims 1, 3-7, 10-13, 16, 38, 39, and 41 remain rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Bawendi et al. (U.S. Patent No. 6,306,610; hereinafter "Bawendi") in view of the reference of Rothbard et al. (U.S. Patent No. 6,306,993; hereinafter "Rothbard"). In particular, Bawendi was cited for teaching a composition comprising fluorescent semiconductor nanocrystals associated with a molecule or prokaryotic or eukaryotic cells. Rothbard was cited for teaching methods and compositions for transporting drugs and macromolecules across biological membranes by using a conjugate containing a biologically active agent that is covalently attached to a transport polymer. The Final Office Action alleges:

> Since Bawendi and Rothbard both teach using a label such as nanocrystals for cells or cell membrane, it would have been obvious to one of ordinary skills in the art to associate the polymer, which comprises of 6 to 25 subunits of Arg residue, taught by Rothbard to the nanocrystals as a fluorescent label and use in the composition of Bawendi because macromolecules such as peptides and oligonucleotides experience difficulty in passing across the biological membrane and having a polymer as that of Rothbard enhances trans-membrane transport. Furthermore, the nanocrystals of Bawendi can be used a label which associates wtih the polymer to so that measures of biological molecules transported across the biological membrane can be easily detected because the nanocrystals of Bawendi associates with the biological membrane. (Final Office Action, page 4.)

The Final Office Action further alleges:

> Regarding claims 38, 39, and 41, it would have been obvious to one of ordinary skills in the art to package the combined composition taught by Bawendi and Rothbard with instruction for using it for economical convenience since Rothbard teaches packaging the polymer with biological active agent into a kit with instructions for using it. (Final Office Action, pages 4-5.)

In addition, claims 8, 9, 15, and 40 have been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the reference of Bawendi (*supra*) in view of the reference of

Frankel et al. (U.S. Patent No. 5,652,122; hereinafter "Frankel"). Frankel is cited for teaching intracellular delivery of cargo molecules by the use of transport polypeptides which comprise HIV tat protein or one or more portions thereof and which are covalently attached to the cargo molecules. In particular, the Final Office Action alleges:

> It would have been obvious to one of ordinary skills in the art to use the HIV tat peptide for transporting biological molecules across the cell membrane as taught by Frankel and attach it to a fluorescence semicondutor nanocrystal which associates to a cell membrane so that when biological molecules to be transported reach the cell membrane, they can be transported effectively and efficiently with the aid of the tat peptide and their activity or measurement can be detected by the nanocrystals since the nanocrystals have a spectral emission that is tunable to a desired wavelength, and wherein said wavelength provides information about a biological state or event. It would have been obvious to one of ordinary skills in the art to package the combined composition into a kit with instruction of using it for economic convenience since Frankel teaches that the tat polypeptide can be used as research laboratory reagents, either alone or as part of a transport polypeptide conjugation kit. (see col. 7, lines 30-32). (Final Office Action, pages 11-12.)

Applicants respectfully traverse the rejections under 35 U.S.C. § 103 on the following grounds.

To support an obviousness rejection under 35 U.S.C. § 103, "all the claim limitations must be taught or suggested by the prior art." M.P.E.P. § 2143.03. In addition, "the teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure." M.P.E.P. § 706.02.

A. Bawendi in view of Rothbard

Bawendi teaches the use of semiconductor nanocrystals associated with a compound that has affinity for a biological target, including cells or cell membranes. However, Bawendi fails to describe or suggest any method for translocating nanocrystals across the plasma membrane of an intact cell for the purpose of labeling the interior of a cell with semiconductor nanocrystals, as taught in the instant application. In particular, Bawendi fails to disclose or suggest any complex of semiconductor nanocrystals with a cationic polymer that is capable of enhancing transport of a semiconductor nanoparticle across a biological membrane, such as a tat peptide or a cationic polymer having from 5 to 25 contiguous Lys and/or Arg residues, as currently claimed. Complexes of semiconductor nanocrystals with affinity reagents, as described by Bawendi,

would be expected to label isolated components of cells or the exterior of cells. Bawendi provides no motivation for using any compound that would enhance transport of nanocrystals into cells.

The secondary reference of Rothbard also fails to teach or suggest any complex of a semiconductor nanocrystal with a cationic polymer. Rothbard pertains to methods of transporting a biologically active agent across a membrane in order to deliver the biologically active agent to a subject for a therapeutic treatment. In particular, Rothbard defines biologically active agents as metal ions, small organic molecules, and macromolecules such as nucleic acids, peptides, proteins, antibodies, and peptide nucleic acids (see col. 2, lines 18-22; and col. 3, lines 42-62). Nowhere does Rothbard describe or suggest transporting semiconductor nanocrystals across a biological membrane in order to label cells. Although Rothbard does use fluorescently labeled transport peptides, as pointed out by the Examiner (Final Office Action, page 4), the transport peptides were labeled with the conventional fluorophore, fluorescein isothiocyanate (see Example 2), for the purpose of proving that the transport peptides were successfully imported into cells. Rothbard has nothing to do with labeling cells *per se* and provides no motivation for transporting nanocrystals.

As pointed out previously in the response to the Office Action of June 27, 2005, semiconductor nanocrystals are colloidal suspensions having a physical form somewhere between molecular and bulk phase materials. Thus, semiconductor nanocrystals have physical properties distinct from the "biologically active agents" described by Rothbard, and one would not have the reasonable expectation of success that carrier peptides employed to transport metal ions or organic molecules across biological membranes would also successfully transport semiconductor nanocrystals.

Therefore, no combination of the cited references teaches or suggests all the limitations of claims 1, 3-7, 10-13, 16, 38, 39, and 41.

B. Bawendi in view of Frankel

As discussed above, Bawendi fails to teach or suggest any transport polypeptides that would enhance transport of nanocrystals into cells. Frankel, which fails to even mention semiconductor nanocrystals, fails to fill the gaps. Rather, Frankel pertains to transport of

"biologically active cargo" using HIV tat polypeptides. Cargo is defined by Frankel as small molecules or macromolecules, such as polypeptides, nucleic acids, and polysaccharides (col. 5, lines 37-45). Like Rothbard, Frankel fails to teach or suggest any complex of a semiconductor nanocrystal with a transport polypeptide. Nor does Frankel suggest transporting semiconductor nanocrystals across a biological membrane in order to label cells. The Examiner points to col. 42, lines 24-29 of Frankel as supposedly teaching the use of a fluorescent label for the motivation to combine the references. However, the fluorescent label in this case is a rhodamine-conjugated antibody that is not described as transported into cells by the tat peptide. Rather, Frankel describes immunofluorescence assays performed on cells after the tat peptide entered cells in order to show that the transport peptide was successfully imported. The cells are permeabilized with detergent in order to allow entry of the rhodamine-conjugated antibody; thus the fluorescent label is not transported into cells. Frankel is not about fluorescently labeling cells and provides no motivation for using semiconductor nanocrystals.

Therefore, no combination of the cited references teaches or suggests all the limitations of claims 8, 9, 14, 15, and 40.

E. Conclusion

In the instant case, there is no motivation to combine the individual elements of the references in the manner set forth by the Examiner. The motivation to combine the references cannot derive from Bawendi, which does not suggest any complexes with semiconductor nanocrystals that would facilitate transport of nanocrystals into cells. Rothbard and Frankel cannot provide the requisite motivation because both references are entirely silent as to semiconductor nanocrystals. The Examiner points to the use of fluorescent labels by Rothbard and Frankel for the motivation to combine the references (Final Office Action, pages 4 and 5); however, both references describe the use of conventional fluorophores solely for the purpose of proving their transport peptides effectively transported conjugates into cells. The conventional fluorophores used, *i.e.* fluorescein isothiocyanate (see Rothbard, Example 2) and rhodamine (see Frankel, col. 42), have no physical resemblance to a semiconductor nanocrystal and cannot provide the motivation to combine a transport peptide with a semiconductor nanocrystal, which

neither reference mentions. Simply put, the references do not provide the requisite motivation to combine their teachings as set forth in the Final Office Action.

In the absence of some teaching or suggestion in the cited references concerning complexes of semiconductor nanocrystals with cationic polymers capable of enhancing transport of semiconductor nanocrystals across a biological membrane; as described in the present application, the Examiner has presented no more than an improper hindsight reconstruction of the present invention.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of elements that can be individually identified in multiple references. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed

invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458. In the pending case, the Office has not met this burden.

As explained in Section 2143.01 of the MPEP, the mere fact that references can be combined or modified does not render the resultant combination obvious, unless the prior art also suggests the desirability of the combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990). Since the suggestion or motivation to combine the references to arrive at the claimed invention is not in the references, the Examiner is required to cite to some knowledge generally available to one of ordinary skill in the art for the motivation to combine the references. (MPEP 2143). It is respectfully submitted that the Examiner has not provided such knowledge. Instead, the Examiner has merely asserted that because (1) Bawendi teaches complexes of semiconductor nanocrystals with molecules that have affinity for cells or cellular components and (2) Rothbard and Frankel teach transport polypeptides, it would have been obvious to combine the references.

Without a suggestion to modify the references evident in the prior art, as well as a lack of a reasonable expectation of success, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit, "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992). As also stated by the Court of Appeals for the Federal Circuit "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention." *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988). Therefore, the Office has not met the requirements for a *prima facie* showing of obviousness under 35 U.S.C. § 103.

For at least the above reasons, withdrawal of the rejections under 35 U.S.C. § 103(a) is respectfully requested.

CONCLUSION

In light of the above remarks, Applicants submit that the present application is fully in condition for allowance. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned.

The Commissioner is hereby authorized to charge any fees and credit any overpayment of fees which may be required under 37 C.F.R. §1.16, §1.17, or §1.21, to Deposit Account No. 18-1648.

Respectfully submitted,

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